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December 16, 2008

Samuel Wilson, M.D., Acting Director
National Institute of Environmental Health Sciences / National Toxicology Program
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RE: Request for NTP to Fully Consider New Styrene Epidemiology Review Prior to Finalizing Styrene Draft Substance Profile

Dear Dr. Wilson:

On December 15, both the National Toxicology Program (NTP) and the Styrene Information and Research Center¹ (SIRC) received the styrene epidemiology report from Drs. Boffetta (IARC), Adami (Harvard), Cole (University of Alabama), Trichopoulos (Harvard), and Mandel (University of Toronto) [Boffetta et. al.]². I am enclosing a copy of their report and request that it be made a part of the *Report on Carcinogen's (RoC)* styrene docket. This group of world-renown epidemiologists from prestigious institutions worked completely independently of our organization. We had no prior knowledge of their conclusions.

In previous correspondence we have asked that NTP delay the next step in the *RoC* process for styrene (the preparation of the draft substance profile on styrene scheduled for December 24, 2008)

¹ The Styrene Information and Research Center's (SIRC's) mission is to evaluate existing data on potential health effects of styrene, and develop additional data where it is needed. SIRC has gained recognition as a reliable source of information on styrene and helping ensure that regulatory decisions are based on sound science. For more information, visit <http://www.styrene.org>

² Epidemiological Studies of Styrene and Cancer: A review of the Literature, December 9, 2008, Boffetta, P. (International Agency for Research on Cancer, Lyon, France; Vanderbilt University, Nashville, Tennessee), Adami, HO (Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts), Cole, P. (School of Public Health, University of Alabama, Birmingham, Alabama) Trichopoulos, D., Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, and Mandel, J.S. (Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario).

until NTP has had a chance to review this report by Boffetta et.al. *in detail*, and consider its implications for the NTP conclusions regarding styrene. With this report in hand, we now know that Boffetta et.al. have reached conclusions that are diametrically opposed to those reached by the RoC Expert Panel on styrene, whose un-peer-reviewed re-analysis of a published study we have repeatedly criticized and brought to your attention in correspondence.

Boffetta et.al.'s full review of the styrene epidemiological data can be summarized and contrasted with that of the NTP Expert Panel as follows:

Delzell et al (2006) – The NTP Expert Panel reported the strongest evidence comes from Delzell et. al (2006) in styrene-butadiene rubber (SBR) workers, concluding there was an exposure-response relationship for NHL and NHL plus chronic lymphocytic leukemia (CLL) that was not attenuated by control for butadiene and only mildly attenuated by control for dimethyldithiocarbamate. However, Delzell et. al., which was an update of an earlier cohort study conducted by the NTP Panel's Epidemiology Subgroup Chairperson, Dr. Genevieve Matanoski, rejected this conclusion. In effect, the NTP Panel's new conclusion served to validate Dr. Matanoski's earlier findings. *In contrast, Boffetta et. al. concluded that "...an analysis of styrene exposure stratified by 1,3-butadiene or DMDTC exposure did not indicate a consistent pattern of risks for styrene exposure in any category of exposure to the other agents."*

Kogevinas et al (1994a) – Without explaining their criteria, the NTP Panel essentially threw out the studies in reinforced plastics (RPC) workers because they were too small (5000, 15,000, or 40,000 workers) or had too few workers with long-term exposures (but not significantly shorter than the SBR workers). The NTP Panel did, however, cite the RPC study Kogevinas et. Al. (1994a), as providing supportive evidence, concluding increases in RR for all lymphomas with time since first exposure and estimated average exposure in the multi-plant cohort studied by Kogevinas. *In contrast, Boffetta et.al. found: "An association between average level of styrene exposure and NHL risk was **suggested** in the multicenter European study but **no trend** with duration of exposure to styrene (the SMR of NHL for 5 or more years of employment was 1.01 [95% CI 0.27-2.57]) (Kogevinas et al., 1994b) or with cumulative exposure was evident (Figure 2)."*

Overall Conclusion – The NTP Expert Panel concluded that there was "limited" evidence of carcinogenicity in humans, based specifically on Delzell et. al. (2006) and Kogevinas et. al. (1994a). The NTP Panel essentially "upgraded" the findings of these studies by arriving at conclusions about the data that were not reported by the authors themselves. These two new conclusions were then used to meet the threshold requirements for a finding of "limited" evidence. *In contrast, Boffetta et.al. concluded that "The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of cancer."*

The styrene industry has now submitted to NTP four independent evaluations of the styrene epidemiologic data – Boffetta et. al., Teta, Goodman and Rhomberg, and Delzell. All have agreed that

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there is no evidence of a causal association of styrene with any type of cancer in humans.

The Boffetta report plainly shows that there is a legitimate scientific dispute that needs to be resolved in a considered, scientifically sound, and open manner. To do otherwise would raise serious questions about the integrity of the *RoC* scientific process and its dedication to fairness and to the scientific process.

Clearly the findings of these eminent epidemiologists require a re-evaluation of the NTP background document and Expert Panel recommendations. Any serious re-evaluation is incompatible with rushing ahead to incorporate the recommendations of the Expert Panel into the NTP draft substance profile, now scheduled for publication no later than December 24, 2008. We submit that the NTP needs to take the time to consider the conclusions of the Boffetta et.al. report *carefully* and address the inconsistency with the Expert Panel's recommendations, and what this means in terms of classification of styrene under the criteria of the *RoC*. We request again that you delay the development of the draft profile on styrene, remove styrene from the agenda of the February 24, 2009 Board of Scientific Counselors, and take the time needed to address these matters thoroughly in January, rather than rushing to meet the self-imposed deadline of December 24th. We also request that NTP redraft, amend, or supplement the Background document on styrene. As the report by Boffetta et. al. demonstrates, the Expert Panel's conclusions with regard to epidemiology are so fundamental to its recommendation to classify styrene as "reasonably anticipated to be a human carcinogen" that its recommendation can no longer be relied upon in the background document.

We look forward to your prompt response in light of the schedule's impending deadline of December 24th for the publication of the draft profile.

Very truly yours,


Signature



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cc: Dr. Ruth Lunn, Report on Carcinogens, NTP
Dr. Linda Birnbaum, NTP Incoming Director

Attachment: Epidemiological Studies of Styrene and Cancer: A review of the Literature, December 9, 2008, Boffetta, P. et al.